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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,027	02/15/2002	Douglas Richman	11068-008-999	2397

20583 7590 10/03/2003

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 10/03/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,027	RICHMAN ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,41-45 and 52-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,41-45 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election of Group I (claims 38, 41-45 and newly added claims 52-57) in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper No. 7, is attached to the instant Office Action.

Drawings

The drawings are objected to, please see Notice of Draftsperson's Review attached to the instant Office Action. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42, 45, 52 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are not clear, how can the nucleic acid encoding the patient envelope protein be in the same expression vector that does not contain any envelope protein? "... a nucleic acid encoding a viral envelope protein...lacks a nucleic acid encoding an

envelope protein" how can it be both? lacking any envelope construct while having a patient derived envelope construct. Clarification of what applicant intends is required.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 38, 41-45, 52-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al. (Journal of Virology, 1996 ; see IDS), Petropoulos et al. (Antimicrobial Agents and Chemotherapy, April 200 ; see IDS) in view of Zhang et al. (Journal of Virology, 1999).

The instant claims are drawn to a method that assays for the ability of antibodies to block viral entry (infection) into a cell. The method comprises taking a sample form a patient and extracting the nucleic acid sequence of HIV viral envelope protein. "comprising" is a term of art used in claim language that means the named elements are essential , but other elements may be added and still form a construct within the scope of the claim. The patient derived nucleic acid sequence in conjunction with an indicator vector is transfected into a cell. The indicator vector comprises HIV nucleic acid sequences that lacks the envelope protein. The transfected cell is able to produce viral particles. These viral particles are then tested for their ability to enter into a new cell in the presence of an antibody. If the antibody is able to block the particle entry into the cell the new cells will develop less signal. The second cell is able to expresses a cell surface receptor necessary for particle entry.

Gao et al. teaches the use of a single round virus infectivity assay utilizing patient derived amplified envelope segments. In this assay the patient derived end gene pSVIII-gp160 constructs which expressed functional envelope under the control of HIV-1 LTR promoter. pSVIII-gp160 were co-transfected with HXBH10Δenv Cat into Cos-cells. HXBH10Δenv Cat is an *env* deficient provirus, which contains a chloramphenicol actyltransferase (CAT gene) in place of the *nef* gene. After culturing the Cos cells the produced virions are collected and used to infect new donor derived peripheral blood mononuclear cells (PBMC), the cells were then assayed for the presence of Cat activity (see page 1654, material and methods). The proposed utility for the generated envelope clones includes the use of the constructs for analysis of fusion enhancement *env* complementation and infectivity assays (see page 1665, last paragraph). The reference teaches utilizes a nucleic acid *env* sequence obtained from a patient and co-infecting

cells with this pSVIII-gp160 expression vector comprising the *env* sequence and an envelope deleted provirus, growing the cells and collecting the viral particles. The particles are then used to infect new cells and the infection can be monitored by CAT activity. Though the reference suggests the use of these envelope constructs for studying infectivity the reference does not provide a step-by-step assay for the analysis of a compounds ability to inhibit viral entry (infection) in a permissive cell (a cell that expresses a cell surface receptor).

Petropoulos et al. teach a single cycle transfection assay with HIV vectors in which a patient sample can be tested for the sensitivity to a compound. In this assay the patient derived sample involves the polymerase gene. The reference disclose a resistance test vector that contains *gag-pol* but has the envelope region deleted and the luciferase reporter gene inserted instead. This is referred to as the resistance test vector. The reference uses the amphotophic MLV *env* DNA segment on a second vector. Co transfecting cells with both vectors allows for the production of viral particles that are able to enter (infect) a new cells (see page 922, figure 1). The assay is set up to rescue the risk of recombination thereby reducing the rsik to laboratory personal. The reference teaches an assay that tests for the effectiveness of compounds and their ability to inhibit HIV replication. The assay allows for the monitoring of drug resistance in a patient sample. The assay can be used to screen for new drugs that are active against the HIV resistant strains. The reference does not teach analyzing a patient derived *env* segment for their ability to infect new cells and for compounds that may inhibit the viral entry.

Zhang et al. teach an assay using a patient derived HIV *env* sequence in a pseudovirus construct. And assaying the ability of the pseudovirus to infect cells that express a cell surface receptor to which HIV binds CD4 and either CXCR4 or CCR5. The envelope constuct was

extracted at varying time point in the patient infection. Antibodies where collected at the same time points and assayed for their ability to neutralize the entry of the pseudovirus into the host cell.

It would have been obvious to one of ordinary skill in the art at the time the invention was filed to test patient derived anti-HIV antibody samples for their ability to neutralize viral entry (infectivity) into new cells. One having ordinary skill in the art would have been motivated to monitor the HIV status in a patient in order to provide the most directed treatment based on the HIV status in the patient. Different *env* sequences have different biological effects and ability to enter the host cells based on their ability to bind the host cell rectors. Determining if a patient derived virus has mutated to such a degree that it evades the neutralizing antibody response of the host and thereby requires a change in the treatment is disrable to optimize treatment protocols. Viruses that have diminished capacity to enter a new host cell are found in long terminal HIV survivors, indicating that reducing the ability of a particle to enter the next host cell will be beneficial for increasing the survival of an HIV infected person. The ordinary artisan at the time the invention was made would have known that envelope protein is an important player in the HIV viral life cycle, the envelope proteins are expressed on the surface of the viral particle and are involved in viral docking to the host cell via a cell surface receptor. The manipulation of retroviral sequences is well established, the prior art has shown that *gag, pol* and *env* can be expressed from separate plasmids and still result in virus particle to formation. The prior art has taken envelope deleted HIV constructs and supplemented the construct with a plasmid carrying envelope from aanther stain of HIV or even another virus such as VSV-G. The Zhang et al. reference teaches testing an patient derived antibody sample with a patient derived

envelope construct to determine if there are mutation in the viral envelope during the infection results in a loss of binding to neutralizing antibody over the course of the infection. Optimizing experimental conditions, including the whether the nucleic acid constructs are to be found on an extrachromosomal plasmid or whether they are integrated into he host cell, falls within the skills of an ordinary artisan. If the location of the nucleic acid construct (integrated vs. expression plasmid based) produces an unexpected result, applicant needs to point out what the unexpected results are. Therefore, the instant invention is rejected in view of the cited art.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 or for informal communications use 703-746-3162.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER
9/30/03